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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/710,444	11/10/2000	Lutz Ricchmann	8654/1090	5253

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EXAMINER	
STEELE, AMBER D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/710,444	RIECHMANN ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7 and 9-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7 and 9-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 1, 2007 has been entered.

Status of the Claims

2. The amendment received on April 10, 2006 amended claims 1-3, 8-9, and 20 and canceled claim 4.

The amendment received on March 1, 2007 amended claims 1, 3, 9, and 11 and canceled claims 2 and 8.

Claims 1, 3, 5-7, and 9-21 are currently pending and under consideration.

Election/Restrictions

3. Claims 10 and 12 were withdrawn in the Office action mailed November 10, 2005 as being directed to a non-elected invention (please refer to section 4). However, in view of applicants' arguments and the amendments to claim 1, claims 10 and 12 are rejoined with the elected invention.

4. The status identifiers for present claims 10 and 12 are "withdrawn". However, the status identifiers should be "previously presented". The withdrawn status identifiers will be considered non-compliant if not changed in response to the present Office action.

Priority

5. Receipt is acknowledged of papers (United Kingdom 9810223.9 05/13/1998 and United Kingdom 9810228.8 05/13/1998) submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

6. The priority of the present application is acknowledged as being a CON of PCT/GB99/01526 05/13/1999. In addition, foreign priority to United Kingdom 9810223.9 and United Kingdom 9810228.8 is acknowledged.

Withdrawn Objections

7. The objection to the claims 11 and 12 regarding clarification that only some proteins are unfolded is withdrawn in view of applicants amendments to the claims received on March 1, 2007.

8. The objection to claim 2 is objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the cancellation of claim 2 in the amendment received on March 1, 2007.

9. The objection to claim 8 as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the cancellation of claim 8 in the amendment received on March 1, 2007.

Maintained Rejections

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Please note: the rejections have been altered to reflect the claim amendments received on March 1, 2007.

Claim Rejections - 35 USC § 112

11. Claims 1, 3, 5-7 and 9-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 1 is drawn to a method for the selection of a virus comprising (a) providing a plurality of virions encoding and displaying a fusion polypeptide comprising a heterologous polypeptide inserted into the sequence of a viral coat protein polypeptide with a cleavable site within the displayed polypeptide and wherein cleavage of the cleavable site impairs infection by a virion, (b) exposing the virus to a protease which cleaves improperly folded fusion polypeptides, and (c) propagating a virion comprising intact fusion polypeptide. The invention as claimed encompasses all known fusion proteins and all potential fusion proteins since virtually any protein can be cleaved. The claimed invention states that cleavage of the cleavable site impairs infection. The claimed invention does not include any structural information regarding

the cleavage site, the location of the cleavage site in the fusion polypeptide, or the specificity of the protease. In addition, the claimed invention does not include any structural information regarding folding of the polypeptide that could prevent cleavage by protease. The structural limitation that the protease is specific for the cleavage site and not for any other location in the polypeptide is not present in the claimed invention.

The specification teaches that the cleavage site should be absent from the virus other than at the cleavage site or inaccessible to cleavage and may be part of the coat protein (please refer to page 4, lines 19-26; pages 9, 11). In addition, the specification also teaches proteases including trypsin, chymotrypsin, thermolysin, subtilisin, Glu-C, and Factor X as the cleaving agent (please refer to page 9). The specific cleavage residues of the proteases are listed (please refer to page 9). However, the claimed invention does not include the structural limitations of the particular residues or structural limitations regarding how the cleavage sites are made inaccessible. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the invention as claimed since every known and unkown heterologous polypeptide, every known and unknown viral coat protein, every known and unknown fusion protein, (e.g. conservatively billions), every known and unknown virion (e.g. conservatively thousands), and every known or unknown protease cleavage site is encompassed by the presently claimed method. Furthermore, not all proteases are expected to provide similar results regarding inhibition of viral infectivity and any protease which lacks impairment of infectivity may not be solely due to proper protein folding (please refer to page 15, Example 2 wherein Factor X, Arg-C, and thrombin did not lead to a loss in infectivity despite the presence of cleavage sites and the lack of a properly folded fusion polypeptide). Therefore, the method as presently claimed would

not necessarily lead to the propagation of only intact fusion polypeptides dependent on the cleavage site and the protease.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of the cleavage site (e.g. SEQ ID NO: 1; please refer to example 2) utilized with trypsin, thermolysin, subtilisin, Glu-C, or chymotrypsin (Example 2) as disclosed by the specification, the skilled artisan cannot envision the entire scope of the method of claim 1 was in applicants possession. In addition, the polypeptides barnase (e.g. mutant A) and villin are the only examples of properly folded polypeptides that make the cleavage site inaccessible and allows for viral propagation (please refer to examples 5-6). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

Arguments and Response

12. Applicants' arguments directed to the rejection under 35 USC 112, first paragraph (written description), for claims 1, 3, 5-7 and 9-21 were considered but are not persuasive for the following reasons.

Applicants contend that the specification teaches the position of the cleavable site in the virus. Applicants cite page 4, lines 19-26; page 5, lines 28-30; and page 6, lines 20-30 of the present specification for support. In addition, applicants contend that the specification teaches how the protease cleavage sites may be incorporated into the coat protein and where the protein should be inserted. Applicants cite page 9, lines 15-26 of the present specification for support. Applicants also acknowledge the examiner's statement that some proteases and some protease cleavage sites are provided by the applicant (i.e. trypsin is art recognized to cleave at Lys and Arg residues; chymotrypsin is art recognized to cleave at Phe, Trp, Tyr, and Leu residues; thermolysin is art recognized to cleave at small aliphatic residues; subtilisin is art recognized to cleave at small allopathic residues; Glu-C is art recognized to cleave at Glu residues; Factor Xa is art recognized to cleave at Ile/Leu-Glu-Gly-Arg, Arg-C is art recognized to cleave at Arg residues).

Applicants' arguments are not convincing since applicants have not supplied adequate written description for the vast genuses presently claimed (i.e. required for performing the method steps as currently claimed). While, written description takes into account the entire disclosure of the specification, it is the breadth of the claims which must be adequately described. In addition, applicant is reminded that limitations appearing in the specification but not recited in the claim should not be read into the claim [please refer to E-Pass Techs., Inc. v.

3Com Corp., 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) which states: claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily; please also refer to MPEP § 2106]. Thus, any structural limitations found in the specification cannot be read into the claims.

Applicants cite several passages (see below) from the specification as support for written description of the scope of the presently claimed method. It is noted that the passages provide general guidance and not specific structural information regarding the virus, virus coat protein, protease, polypeptide, fusion polypeptide, and/or cleavage site.

Page 4, lines 19-26: A "cleavable site" is a site capable of cleavage when exposed to a cleaving agent. In the present invention, the use of protease cleavage sites, capable of being cleaved with proteases, is preferred. Protease cleavage sites may be part of, or incorporated in, polypeptides according to the invention; alternatively, it may be independently engineered into the coat protein of the virus. A feature of the cleavable site is that it should either be absent from the virus other than at the site of its specific insertion according to the present invention, or otherwise inaccessible to cleavage, or present only in viral proteins which are not required after virion assembly to mediate infection.

Page 5, lines 28-32: A tag is any suitable entity capable of binding to a ligand which may be used to isolate a virus by the method of the present invention. Accordingly, the tag is resistant to the cleaving agent used in the method of the invention. Examples of tag/ligand pairs include barnase/barstar, avidin/biotin, antibody or antibody fragments and ligands, chelating groups and chelates, for example metals, and the like.

Page 6, lines 20-30: The cleavable site is advantageously located in or adjacent to the heterologous polypeptide, such that it can be protected by folding of the heterologous polypeptide and thus allow selection for heterologous polypeptides which are capable of correct folding. Alternatively, however, the cleavable site may be located distal to the heterologous, polypeptide; in such embodiments, the cleavable site may serve to permit reduction of background in phage display techniques. For example, introduction of the cleavable site into helper phage used with phagemid encoding a repertoire of polypeptides allows helper phage to be removed by cleavage prior to infection of host cells, thus dramatically reducing background due to "empty" phage. Advantageously, therefore, the cleavable site is incorporated into the virus coat protein.

Page 9, lines 15-26: Protease cleavage sites may be incorporated into the coat protein of a virus by constructing a fusion between the coat protein and a further polypeptide, the further polypeptide containing the cleavage site. The further polypeptide should be inserted at a position in the viral coat protein such that it allows the assembly of a functional viral capsid and subsequent infection, but if cleaved will result in the impairment of infectivity. If the protease

cleavage site incorporated in the coat protein remains uncleaved, therefore, the virus is capable of assembly into functional virions and retains the potential to infect host cells. If the protease cleavage site is cleaved, however, the structure of the viral coat protein will be compromised and the virus will lose at least part of its potential to infect host cells.

Thus, the passages (see above) do not provide any specific structural information about the virions, the virus coat protein, protease, polypeptide, fusion protein, or cleavage site. In addition, the passages (see above) state that the cleavage site can be in the coat protein or the polypeptide portion of the fusion protein (i.e. not specific structural information).

Regarding the "laundry list" of potential proteases and protease cleavage sites, applicant is respectfully directed to Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) which states: a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. Please also refer to § MPEPE 2163.

Moreover, applicants showed in the present specification specific examples of non-working embodiments utilizing proteases (please refer to page 15, Example 2 wherein Factor X, Arg-C, and thrombin did not lead to a loss in infectivity despite the presence of cleavage sites and the lack of a properly folded fusion polypeptide). MPEP § 2163 states that "for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession." In addition, MPEP § 2163 also refers to Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) regarding written description of genuses in biotechnology arts which states: "a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results

obtained from species other than those specifically enumerated. Furthermore, In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004) states that "[a] patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed."

13. Claims 1, 3, 5-7 and 9-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of selection of a virus comprising providing a virus encoding and displaying barnase mutant A or villin with a cleavage site (e.g. SEQ ID NO: 1), exposing the virus to trypsin, thermolysin, subtilisin, Glu-C, or chymotrypsin (e.g. cleaving agents), and propagating virus comprising a polypeptide folded in a manner that makes the cleavage site inaccessible, the specification does not reasonably provide enablement for a method of selection of a virus utilizing any known or unknown cleavage site, any known or unknown cleaving agent, and any known or unknown polypeptide. The specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claim. This is a **scope of enablement** rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;

4. The level of skill in the art;

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The presence or absence of working examples;

8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

The claims include any virus that can express a fusion polypeptide including surface display via phage; any cleavage site regardless of specificity for a particular cleaving agent; any cleaving agent including agents with a specific cleavage residue, agents with nonspecific cleavage residues, chemicals, enzymes, drugs, reducing agents, etc.; any known or unknown fusion polypeptide. Accordingly, the claims encompass the selection of a vast number of virus particles expressing a vast number of fusion polypeptides. Accordingly, the claim scope is unduly broad with respect to encompassed polypeptides, virions, cleavage sites, and cleaving agents.

The state of the prior art and the level of predictability in the art:

While the state of the art and level of predictability for the expression of fusion proteins in virus particles (e.g. phage display) and screening assays based on binding is high, the art is silent at the time of the disclosure with regard to correlating a decrease in viral infectivity with improper protein folding including which cleavage sites and cleaving agents would be advantageous in the method. The state of the art in July 1998 reported that not all cleaving agents

produced the expected result of decreasing viral infectivity. Kristensen and Winter (Folding & Design 3: 321-328, 1998) teach that a cleavage site with several proteolytic sites was susceptible to cleavage by trypsin, thermolysin, subtilisin, Glu-C, and chymotrypsin but infectivity of the virus was not altered by Factor Xa, Arg-C, or thrombin even though potential cleavage sites were present (please refer to pg. 322). In addition, Kristensen and Winter note that several limitations to the method are present including phage must be resistant to the digestion conditions, protein must be exported to the surface, the cleavage site must be specific for a chosen protease, and the fusion protein must cleave after nicking without noncovalent attachment (pg. 324). Please also refer to Example 2 of the present specification. Furthermore, Sieber et al. (Nature Biotechnology 16: 955-960, October 1998) teach that correlating proteolytic stability with infectivity of filamentous phage is best suited to compact monomeric proteins and consideration of the phage stability and the specific protease utilized is necessary (please refer to pg. 958-959).

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

The specification provides examples of two fusion proteins that can be utilized to make the cleavage site inaccessible via folding, provides one cleavage site construct, and five of eight cleavage agents utilized in a control experiment would be useful for additional experimentation (examples 2, 5, and 6).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to produce additional cleavage sites, experiment with additional denaturing conditions dependant of the stability of the naïve protein, experiment with various cleaving agents especially if agents outside the genus of proteases are utilized wherein even some of the preferred embodiment of proteases were found to be nonfunctional in the method, and take into consideration the stability of the virus utilized.

Therefore, the presently claimed invention is not enabled for the scope of the claimed method.

Arguments and Response

14. Applicants' arguments directed to the rejection under 35 USC 112, first paragraph (scope of enablement), for claims 1, 3, 5-7 and 9-21 were considered but are not persuasive for the following reasons.

Applicants contend that the specification has provided clear guidance for one of skill in the art to choose a protease and the known target sequences of those proteases. In addition, applicants contend that the Kristensen et al. reference and Example 2 of the present specification teaches that if a flexible linker is inserted between domains 2 and 3 of the phage coat protein pIII the previously nonsensitive phage becomes sensitive to cleavage (page 322 and Figure 1 of Kristensen et al.). Furthermore, applicants contend that Sieber et al. teach a proside method that

does not teach away from the methods of correlating proteolytic stability with either monomeric or globular proteins.

Applicants' arguments are not convincing since the "clear guidance" equates to a "laundry list" of potential proteases. Regarding the specific structural limitations taught in Example 2 of the present specification and the Kristensen et al. reference regarding the ability of the linker inserted between domains 2 and 3 to make non-cleavage sensitive phages cleavable, it is noted that proteases including Factor Xa, Arc-C, or thrombin still did not cleave these constructs or lead to a loss in viral infectivity despite the presence of potential cleavage sites for these enzymes (please refer to page 322 of Kristensen et al.). Regarding Figure 1 of Kristensen et al., only trypsin is utilized as the protease in the experiments of Figure 1. Regarding the Sieber et al. reference, the reference is utilized to teach the various considerations (i.e. predictability in the art) necessary for performing the presently claimed method including selection of stable virus (i.e. phage), stability of the polypeptide in various assay conditions (e.g. buffers, etc.), composition of the polypeptide (e.g. Sieber et al. states that the method is best suited to monomeric proteins while large multidomain proteins or proteins with flexible regions would be more difficult to utilize in the method; please refer to page 958, right column, last full paragraph), and properties of the specific protease utilized.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
June 6, 2006

MARK L. SHIBUYA
PRIMARY EXAMINER